A REPORT ON
A PHYSICS DIVISION CORE PROGRAM
OF
NATIONAL CENTER FOR THEORETICAL SCIENCES

BIOLOGY INSPIRED THEORETICAL SCIENCES (BITS)

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presented by

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The era of molecular biology began with a physicist

> ”We shall assume the structure of a gene to be that of a huge molecule, capable of only discontinuous change, which consists in the rearrangement of the atoms and leads to an isomeric molecule. The rearrangement may affect only a small region of the gene, and a vast number of different rearrangements may be possible.”

Schrödinger
What is Life? Ch. 5 (1944)

The Human Genome Project

The rapid progress and successes of the Human Genome Project have fundamentally altered the landscape of research in the life sciences. Huge bodies of biological data including DNA and protein sequences now exist in public databanks and the rate of their accumulation is accelerating. The analysis of such data calls for massive cross-disciplinary research efforts involving physical scientists as well and traditional biologists. Many leading research establishments around the world have recognized this need and have responded by setting up new cross-disciplinary research groups, networks and centers.

BITS at NCTS/Physics

- Began as Biology Inspired Theoretical Physics (BITP) Topical Program in 1997 August. Coordinated by TK Lee and HC Lee.
- GOALS
  - To promote cross-disciplinary exchange of ideas between the theoretical sciences and life sciences communities
  - To identify important problems in the life sciences whose solutions theorists in the physical sciences may be able to contribute
  - To foster the formation of vigorous research teams to pursue such solutions
  - To create a favorable environment for the function of such teams
- Proposal after 2000: continue as BITS Core Program. Coordinated by HC Lee.

SUMMARY of ACTIVITIES

1997/10 to 2000/01

- MEETINGS WITH BIOLOGY COMMUNITY (1997/10-1998/11)
- MINI-WORKSHOPS, WORKSHOPS AND SCHOOLS
- NETWORK OF RESEARCH TEAMS
- LOCAL SEMINAR AND COLLOQUIA
- CROSS-STRAIT AND INTERNATIONAL COLLABORATION
- VISITORS
- JOURNAL PUBLICATIONS

WORKSHOPS AND SCHOOLS

- 1997 December 22-23: **What can theoretical physicists do in biology?**
- 1998 June 15-17: 2nd BITS Workshop (BITS-XSI).
- 1999 Jan 22-23: 3rd BITS Workshop.
- 1999 Mar 3: Mini-workshop to discuss national protein folding research project (coordinator: Sunney Chan).
- 1999 June 7-11: 5th BITS Mtg: **Advanced school on protein**.

Main topics: **protein folding, biological membrane, sequence analysis**. 30-80 participants, number decays with time. Most have small international participation.

NETWORK OF RESEARCH TEAMS

- IPAS, TK Lee, **crystal. analysis**
- NCHC, ZY Su, **protein folding**
- NTNU, CM Chen, **protein-mem. int.**
- NTHU, IC Hsu, **DNA microarray**
- NTHU, TH Lin, **protein structure**
- NCHU, SC Tseng, **bio. seq. analysis**
- NDHU, SC Ke, **enzyme function**
- IBMS*, TH Huang, **struct. bio. (expt)**
- IBMS*, C Lim, **struct. bio. (theory)**
- NCU, PY Lai, **DNA structure**
- NCU, CM Ko, **molecular evolution**
- NCU, HC Lee, **pro. folding, evolution**
- Others (NTU, NCU, NCHU, . . .)

- **Biophysics Society*** of ROC
- Bona fide **biologists** (IBMS, Yang-Ming Med U, NCHU, NTHU, NCU, . . .)

*Research program/existence predates BITS

INTERNATIONAL AND CROSS-STRAIT COLLABORATION

- **HS Chan, U Toronto Med School, protein structure**
- **C Tang, NEC Research (USA), protein structure**
- **R Redfield, UBC, Zoology Dept, bacterial DNA uptake system**
- **H Li, Rockefeller U, protein structure**
- **BL Hao, ITP/Beijing, sequence analysis**
- **ZC Ou-yang, ITP/Beijing, membrane**
- **LF Luo, Inner Mongolia U, evolution**

- **BITS-XSII (2nd Cross-Strain BITS Workshop) Beijing, 2000 May 15-19. Organized by BL Hao and WM**

Zheng. Sponsored by ITP/Beijing, CCAST & NCTS. About 15 people from Taiwan will attend.

VISITORS

The BITS program had a large number of foreign visitors, most in the form of speakers/lecturers to the various workshops/schools. Visitors who came to NCTS for other programs often also participated in BITS activities.

INTERNATIONAL visitors:

Allan Campbell, Stanford U., 1998 June 13-19
HS Chan, U. Toronto Medical School, 1999 June 6-12
G.M. Crippen, UCIC Biochemistry, 1999 June 6-12
Y. Duan, UC San Francisco, 1999 June 6-12
H. Flyvbjerg, Risoe Nat'l Lab., Denmark, 1997 Dec 20-26
T. Head-Gordon, US LASL, 1999 June 6-12
Wen-Hsiung Li, U. Chicago, 1998 June 13-19
Huey-Wen Huang, Rice U., Houston, 1997 Dec 20-26, 1999 Jan 21-25
Tom Ray , ATR Res. Lab., Japan, 1997 Dec 20-26
Rosie Redfield, U. Bristish Columbia, 1998 June 13-19
Wu-Pei Su, University of Houston, 1997 Dec 20-26
Chin-Sheng Ting, University of Houston, 1997 Dec 20-26
Kwok-Yip Szeto, HKUST, 1997 Dec 20-26, 1998 June 13-19
C. Tang, Princeton NEC Research, 1999 June 6-12
W.R. Taylor, UK National Inst. Health Res., 1999 June 6-12
Hao Li, U. Rockefeller, 1999 Jan 21-25

MAINLAND visitors:

B.L. Hao, ITP, Beijing, 1997 Augsut - 1998 July, 1999 June 6-12
Shu-Yu Chang, Inst. Phys., Beijing, 1997 Augsut - 1998 July
Liao-Fu Lo, Inner Mongolia U., 1998 June 13-19, 1999 June 18 - Sept. 30
Feng-Min Ji, Inner Mongolia U., 1999 June 18 - Sept. 30
Ji-Xin Liu, ITP/Beijing, 1998 June 13-19
Hui-Min Xie, Suzhou U., 1998 June 13-19
Wei-Mo Zheng, ITP/Beijing, 1998 June 13-19
Zong-Can Ouyang, ITP/Beijing, 1999 Jan 21-25

LOCAL visitors.

A very large number, of the order of 300 man-events, of researchers of various backgrounds from Taiwan took part in one of more of the workshop/schools. Among these, some are already involved with BITS and some among the others may be viewed as potential future participants. A partial list is:

Sunney Chan, Inst. Chem., AS
Lou-Sing Kan, Inst. Chem., AS
Ming-Jing Huang, Inst. Biomed. Sci. AS
Ming-Huang Huang, Inst. Biomed. Sci. AS
Carmay Lim, Inst. Biomed. Sci. AS
Lan-Yang Chang, Inst. Biomed. Sci. AS
Bai-Chuang Shyu, Inst. Biomed. Sci. AS
Cheng-Kung Chou, Yangming Med. Coll. & Taipei Vet. Hospital
Yung-Cheng Yang, Yangming Med. Coll.
Chung-Hsiung Kuo, Cen. Med. Sci., Taichung Vet. Hospital
Tzu-Bi Shih, Inst. Cell & Microbio., Taipei Med. Coll.
S.C. Lee, Inst. Phys. AS
T.K. Lee, Inst. Phys. AS
Simon-C Lin, Comp. Center & Inst. Phys. AS
Sai-Ping Lee, Inst. Phys. AS
Darwin Chang, Phys. NTHU
Ian C.Y. Hsu, Nucl. Sci., NTHU
Ching-ong Wu, Phys. NTHU
Shiyang Chang, EE, NTHU
Thy-Hou Lin, Life Sci., NTHU
Zheng-Yao Su, NCHC
Jean-Fang Guan, NCHC
Chang-Huan Hsieh, NCHC
Chi-Ting Shih, NCHC
Ji-Chin Chang, NSCNU
Chi-Ming Chen, Phys. NNU
San-Ho Chou, Inst. Biochem., NCHU
Nien-Tai Hu, Inst. Biochem., NCHU
Li Lin, Phys. NCHU
Hsen-Che Tseng, Phys. NCHU
Chung-Yi Lin, Phys. NCHU

Ming-Chi Shih, Phys. NCHU
Yen-Chi Tsai, Phys. NCCU
Fang-Yu Chen, Phys. & CCS, NCU
David C.Y. Lu, Phys. & CCS, NCU
Lin I, Phys. & CCS, NCU
Tzu-Min Hsu, Phys. NCU
San-Chiang Lai, Phys. NCU
James Nester, Phys. & CCS, NCU
Hsin-Heng Wu, Phys. NCU
H.C. Lee, Phys. & CCS,
Chung-Ming Ko, Phys. & CCS, NCU
Ming-Sheng Wang, Phys. & CCS, NCU
Pik-Yin Lai, Phys. & CCS, NCU
Pei-Long Chen, Phys. & CCS, NCU
Zhen Ye, Phys. & CCS, NCU
Pi-Gang Luan, Phys. & CCS, NCU
Zi-Hao Wang, Phys. & CCS, NCU
Bai-Hsiang Wang, Phys. & CCS, NCU
Li-Ching Hsieh, Phys. & CCS, NCU
Chi-Yu Chao, Phys. & CCS, NCU

THE NEXT 3 YEARS

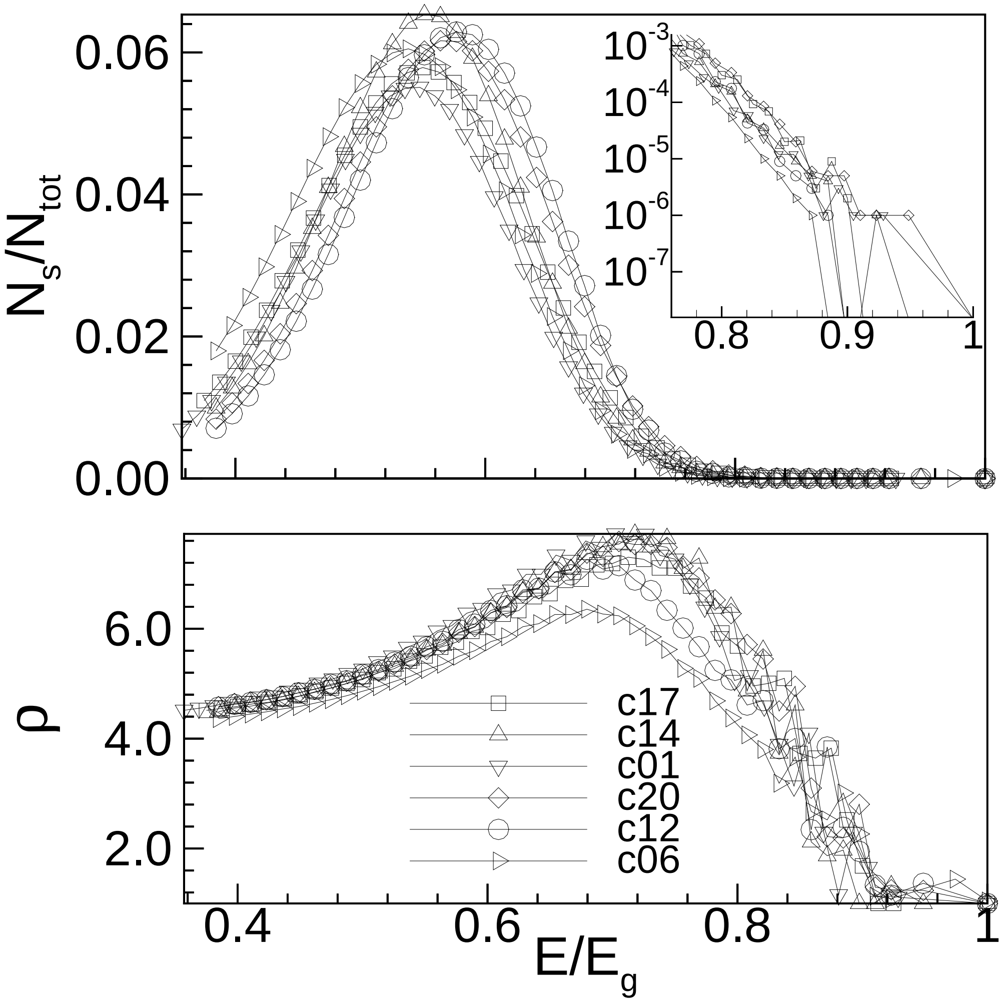
- **Research Direction**
  - Crystallograpgy. Better and faster method to extract structure from data.
  - Protein and protein membrane systems. Closer contact with biologists, physiologists, drug designers. Work with more realistic systems.
  - Evolution. Details mechanism tested on specific cases.
  - ...
  - Genomics. Gene recognition and functional genomics.
  - DNA microarrays. Probe design and data analysis.
- **Activities**
  - 1-2 day intensive topical mini-schools (about 5/year); one or two workshop per year to review progress; longer-term visitors (senior and pdf); short-term visitors; bi-weekly group discussion and journal club meetings; special courses as need arises.
- **Budget (NT$1,500,000/a)**

– Mini-schools ($62K×5)	310,000
– Workshops	500,000
– Long-term visitors (NSC application)	-
– Short-term visitors ($60K/visitor×8)	480,000
– Journal club meetings ($.5K×15×20 mtgs)	150,000
– Incidentals & Contingencies	60,000

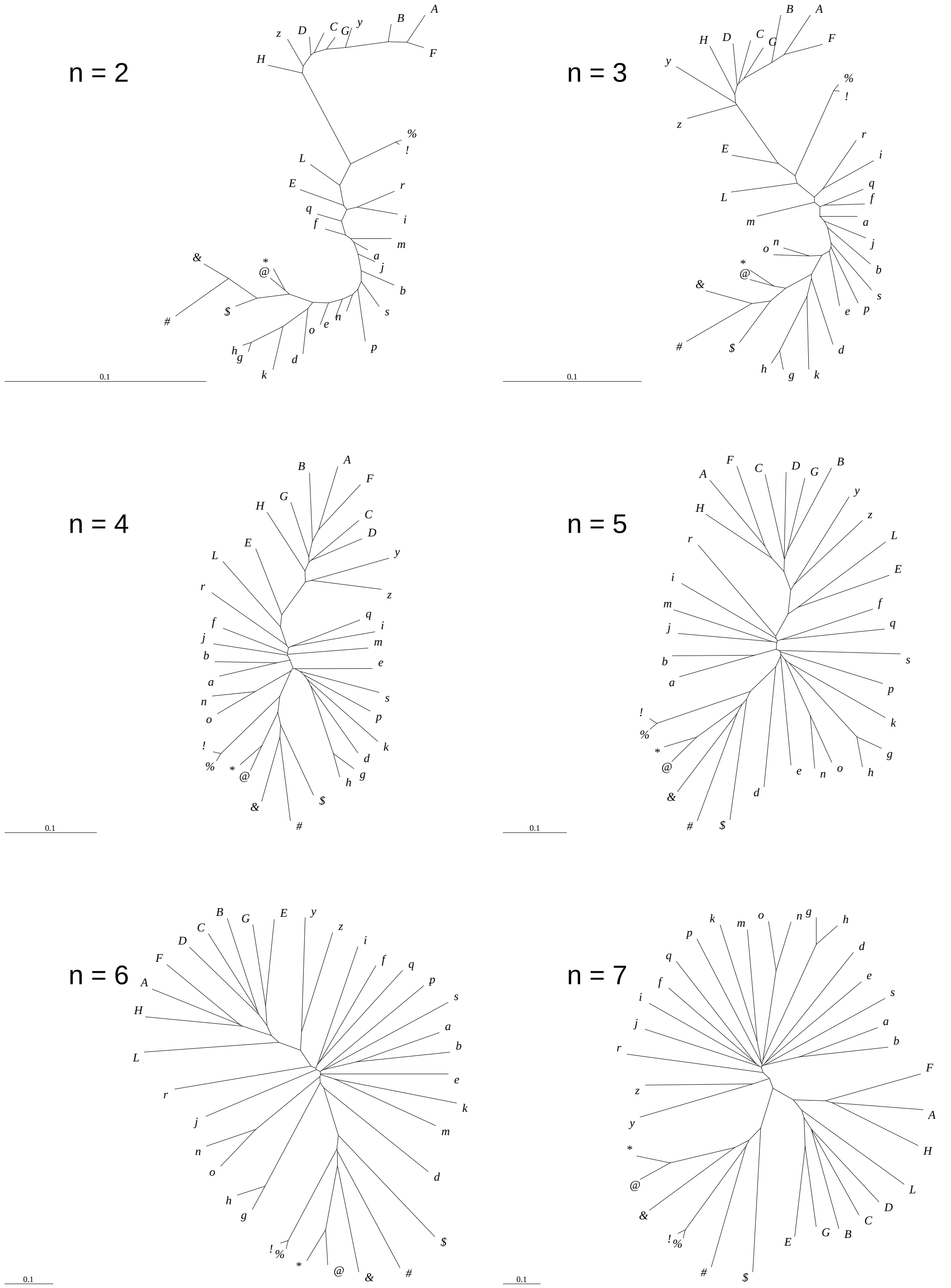
PUBLICATION/PREPRINTS

- Theory for bending anisotropy of lipid membranes and tubule formation C.-M. Chen, Phys. Rev. E, 59, (1999) 6192.
- Histogram Monte Carlo Simulation on Phase Transitions in Polymer Systems, Pik-Yin Lai, Macromol. Theory Simul. (Feature Article) 8, (1999) 382-390.
- Common structural folds in several protein pairs searched by an iterative superposition algorithm. T.H. Lin, J.J. Lin, W.J. Peng and J.H. Liu, Computers Chem. 23, (1999) 109-119.
- Clustering peptide structures through identification of commonly exposed groups. T.H. Lin, J.J. Lin, Y.F. Huang and J.H. Liu, J. Chem. Inf. Comput. Sci. 39, (1999) 622-629.
- Phase coexistance of complex fluids In shear flow, P.D. Olmsted and C.-Y.D. Lu, Faraday Discussion, 1999.
- Nature of driving force for protein folding Z.H. Wang and H.C. Lee, Phys. Rev. Lett., 84 (2000) 574-577
- Mean-field HP model, designability and alpha-heliecs in protein structures C.T. Shih, Z.Y. Su, J.F. Guan, B.L. Hao, C.H. Hsieh and H.C. Lee, Phys. Rev. Lett., 84 (2000) 386-389
- Fractal related to long DNA sequences and complete genomes B.L. Hao, H.C. Lee and S.Y. Zhang, Chaos, Solitons and Fractals, 11 (2000) 825-836.
- Theory for the bending rigidity of protein-coated lipid membranes C.-M. Chen, Physica A, (accepted, 2000).
- Thickening broken and critical fluctuation of phospholipid bilayers. W. C. Hung and F. Y. Chen, (Submitted to Chinese J. Phys.)
- Osmotic threshold and water association for phospholipid gel phase bilayers. W. C. Hung and F. Y. Chen, (Submitted to Chinese J. Phys.)
- Hydration dependence of the hydrophobic thickness and lateral compressibility of phospholipid bilayers. W. C. Hung, F. Y. Chen and H. W. Huang, (Submitted to Biophys. J.)
- Formation and structure of funnel in protein folding. ZY Su, JF Gwan, CT Shih and HC Lee, (in preparation)

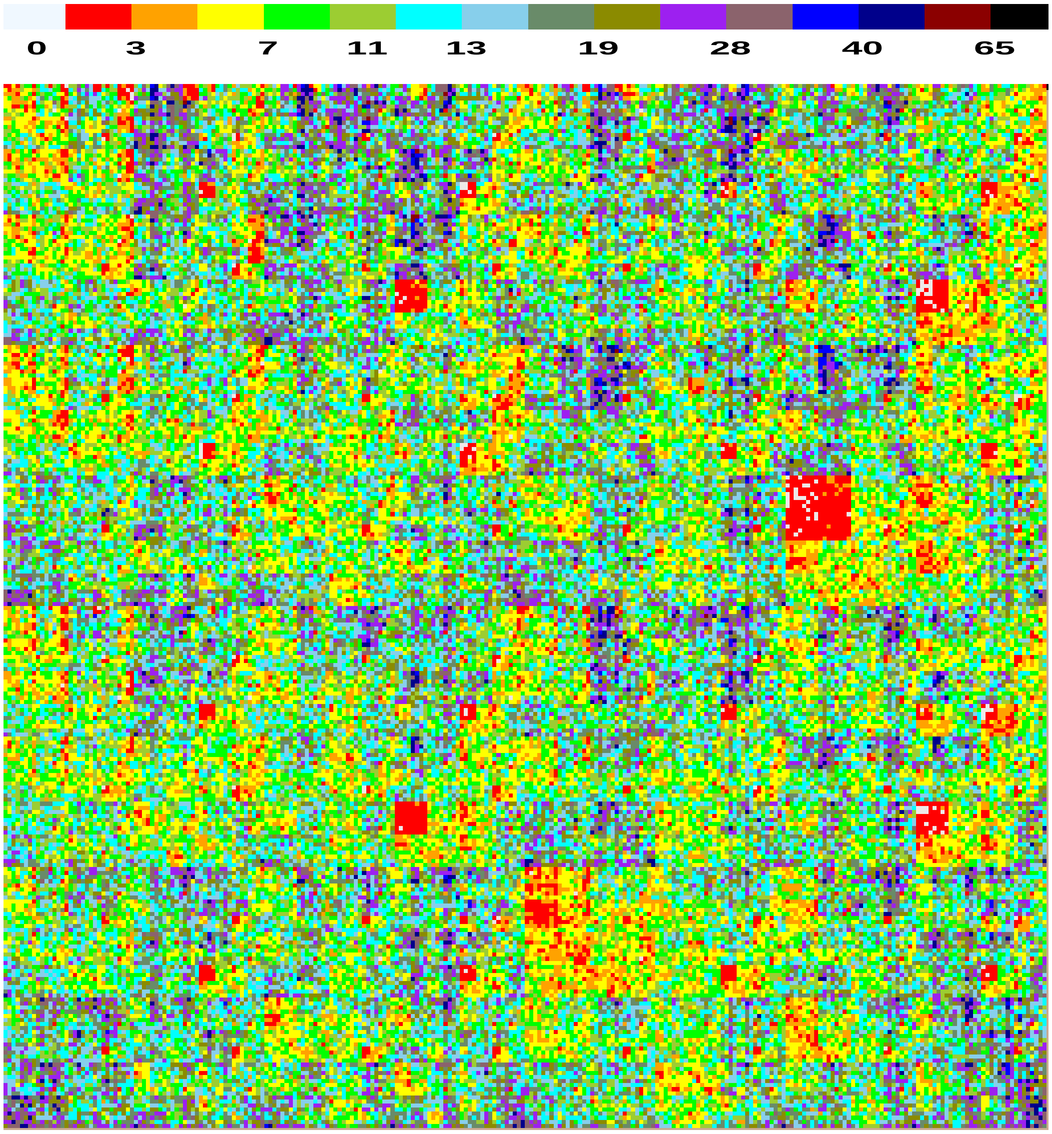
- **Frequencies of oligonucleotides as a means of characterizing organisms L.F. Luo, F.M. Ji, L.C. Hsieh and H.C. Lee, (in preparation)**



Monte Carlo simulation of folding of 25-residue peptides. **Top frame**: Fractional number of states visited by a folding peptide vs relative binding energy. Each symbol corresponds to a different peptide sequence. **Bottom frame**: Bias parameter ρ of visited states vs relative binding energy; larger value of ρ implies stronger bias in concentration in the number of visits to states.



Unrooted **Trees of Life** based on comparing frequencies of oligonucleotides of length n in the 16S rRNA sequences of 38 organisms. Lower case letters: Bacteria; upper case: Archaea; symbols: Eukarya.



E. coli

Fractal structure of “portrait” of the genome of *Escherichia coli*. Each pixel in 256×256 array gives color-coded frequency of one of the 4^8 oligonucleotides of length 8 appearing in the genome.